REVIEW ARTICLE

Pharmacoeconomics 2011; 29 (2): 107-131
1170-7690/11/0002-0107/$49.95/0

Cost Effectiveness of Treatments for Wet Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is a leading cause of blindness in people aged ≥50 years. Wet AMD in particular has a major impact on patient quality of life and imposes substantial burdens on healthcare systems. This systematic review examined the cost-effectiveness data for current

therapeutic options for wet AMD. PubMed and EMBASE databases were searched for all articles reporting original cost-effectiveness analyses of wet AMD treatments. The Centre for Reviews and Dissemination and Cochrane Library databases were searched for all wet AMD health technology assessments (HTAs). Overall, 44 publications were evaluated in full and included in this review.

A broad range of cost-effectiveness analyses were identified for the most commonly used therapies for wet AMD (pegaptanib, ranibizumab and photodynamic therapy [PDT] with verteporfin). Three studies evaluated the cost effectiveness of bevacizumab in wet AMD. A small number of analyses of other treatments, such as laser photocoagulation and antioxidant vitamins, were also found.

Ranibizumab was consistently shown to be cost effective for wet AMD in comparison with all the approved wet AMD therapies (four of the five studies identified showed ranibizumab was cost effective vs usual care, PDT or pegaptanib); however, there was considerable variation in the methodology for cost-effectiveness modelling between studies. Findings from the HTAs supported those from the PubMed and EMBASE searches; of the seven HTAs that included ranibizumab, six (including HTAs for Australia, Canada and the UK) concluded that ranibizumab was cost effective for the treatment of wet AMD; most compared ranibizumab with PDT and/or pegaptanib. By contrast, HTAs at best generally recommended pegaptanib or PDT for restricted use in subsets of patients with wet AMD. In the literature analyses, pegaptanib was found to be cost effective versus usual/best supportive care (including PDT) or no treatment in one of five studies; the other four studies found pegaptanib was of borderline cost effectiveness depending on the stage of disease and time horizon. PDT was shown to be cost effective versus usual/best supportive care or no treatment in five of nine studies; two studies showed that PDT was of borderline cost effectiveness depending on baseline visual acuity, and two showed that PDT was not cost effective. We identified no robust studies that properly evaluated the cost effectiveness of bevacizumab in wet AMD.

Age-related macular degeneration (AMD)/age-related maculopathy (ARM) refers to pathological changes in the central area of the retina that can occur in people aged ≥50 years.[1] Many people who have these changes do not experience symptoms; however, progressive alterations can lead to late-stage ARM (this stage is then referred to as AMD) and vision loss. The form of late-stage AMD most likely to cause blindness is neovascular exudative disease (also termed wet AMD).[2] Wet AMD can be designated classic or occult according to its features on fluorescein angiography, with AMD lesions classified as either 100% classic, predominantly classic (in which choroidal neovascularization [CNV] accounts for at least 50% of the lesion), minimally classic (where CNV accounts for part of but <50% of the lesion) or occult (where there is no CNV).[2]

Symptoms of wet AMD often begin with central visual blurring, distortion (metamorphopsia) or a dark central patch (scotoma), although, if only one eye is affected, these features may not be noticed for some time. When the second eye becomes affected, patients suddenly lose the ability to read, drive or see fine details such as facial expressions and features. AMD (both wet and dry) is one of the leading causes of blindness in the Western world and, because AMD affects older people, its prevalence is set to increase with the rising average age of populations. Indeed, it has been estimated that by 2020 the prevalence of AMD will be three times greater than it was in

1995, with up to 7.5 million people aged >65 years likely to be affected by AMD-related visual impairment.[3]

Costs associated with visual impairment are considerable, and include medical care, loss of income and paid home help. A 2006 study in France[4] estimated that total country-wide non-medical costs of visual impairment were €9800 million per annum. A similar study in Australia[5] estimated that the 2004 cost for vision disorders was Australian dollars ($A)9850 million. A further study estimated total annual non-medical costs of visual impairment to be €10 749 million, €9214 million, €12 069 million and €15 180 million in France, Germany, Italy and the UK, respectively (year 2004 values).[6]

The most commonly used current treatment options for wet AMD are laser photocoagulation, photodynamic therapy (PDT) and intravitreal injections with inhibitors of vascular endothelial growth factor (VEGF)-A. Laser photocoagulation aims to prevent further vision loss by destroying the neovascular complex; PDT is based on a similar concept but involves using a photosensitive agent (usually verteporfin), given intravenously. This agent is activated by laser light (689 nm wavelength) directed to the CNV lesion and causes damage to vascular endothelial cells and thrombotic occlusion of the blood vessels, while reducing concurrent damage to the overlying retina. New pharmaceutical treatments approved for wet AMD are directed against VEGF-A; for example, ranibizumab (a monoclonal antibody fragment) and pegaptanib (a synthetic oligonucleotide) inhibit the biological activity of VEGF-A, thereby aiming to reduce angiogenesis and stall AMD progression.[7-9]

Anti-VEGF treatments for wet AMD have recently been the subject of intense scrutiny; although they have revolutionized the treatment of the condition, offering increases in visual acuity over traditional therapies in the majority of patients, they come at increased costs. Several economic analyses have thus been conducted by both health economists and ophthalmologists to evaluate the cost effectiveness of wet AMD treatments; in addition, because of the implications for medical and social care, healthcare authorities around the world have commissioned their own health technology assessments (HTAs). The aim of this review is to examine the available cost-effectiveness data for the current therapeutic options for wet AMD by conducting a systematic search of the scientific literature and reimbursement authority-authorized HTAs.

1. Literature Review

1.1 Methods

A search of the PubMed and EMBASE databases was conducted in November 2009 using the following search terms: (i) macular degeneration[MeSH] AND (cost-benefit analysis[MeSH] OR economics[MeSH]); (ii) [wet OR neovascular] AND 'macular degeneration' AND cost. No other limits were imposed on the search. All articles published before or during November 2009 were eligible for screening. Titles and abstracts of all articles were screened by two reviewers.

In addition, the HTA databases and UK NHS Economic Evaluation Databases (EED) at the Centre for Reviews and Dissemination (CRD), University of York, and the Cochrane Library were searched in May 2010 to identify HTAs using the following search terms: (Macula OR Macular OR Retina OR Retinal OR Subretinal OR Choroidal OR AMD OR ARMD). All HTAs published before or during May 2010 were eligible for screening. The titles and/or abstracts of all identified records were screened manually by two reviewers for potential inclusion in the review.

The full texts of the identified publications were obtained and screened manually to select those that contained novel cost-effectiveness assessments, and those that were full HTAs (regardless of whether the HTAs contained original cost-effectiveness assessments). Data from publications that met these criteria were extracted into the tables included in this review. Studies that reported purely cost data (e.g. burden-of-illness studies, cost-of-illness studies) or that were reviews of previous cost-effectiveness evaluations, were excluded. Where possible, foreign language publications were translated in order to gather the required information.

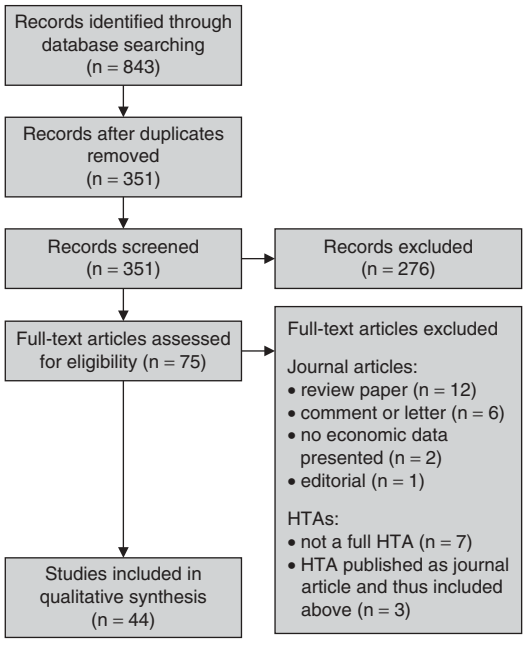

Fig. 1. Flow of the systematic review process. **HTA** = health technology assessment.

1.2 Results

The flow of the systematic review process is presented in figure 1. In total, 843 publications were identified by searching the PubMed, EMBASE, CRD and Cochrane Library databases. After eliminating duplicates, 351 unique publications were identified, and 75 warranted further investigation. Of the 276 articles excluded based on the title/abstract, most were not cost-effectiveness studies/HTAs of wet AMD treatments. The remainder were opinion, comment or letter articles, review articles, foreign language publications with no translation, or did not contain any pharmacoeconomic data.

The studies identified in our analysis employed a broad range of methodologies, perspectives and assumptions, which made comparisons between studies difficult. A summary of the studies is provided in the Supplemental Digital Content 1, http://links.adisonline.com/PCZ/A100. Most studies expressed the results in terms of cost per QALY gained (i.e. most studies involved cost-utility analyses). Other cost-effectiveness measures included the cost per vision-year gained, cost per line-year gained (using either the Snellen or, mostly, the ETDRS chart) [see table I for full study names] and cost per case of blindness prevented. The majority of economic analyses used a second (better-seeing) eye model. This model assumes treatment is not initiated until the second eye is affected; effective treatment thus has a greater impact on visual

Table I. Study acronyms and names

Study acronym	Study name
ABC	Avastin (Bevacizumab) for Choroidal neovascular age-related macular degeneration
ANCHOR	ANti-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularization in age-related macular degeneration
AREDS	Age-Related Eye Disease Study
CATT	Comparison of Age-related macular degeneration Treatments Trial
ETDRS	Early Treatment Diabetic Retinopathy Study
IVAN	A randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization
MARINA	Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular Age-related macular degeneration
MICMAC	MICroeconomics of MACular degeneration
MPS	Macular Photocoagulation Study
PIER	Phase 3b, multi-centre, randomized, double-masked, sham Injection-controlled study of the Efficacy and safety of Ranibizumab in subjects with subfoveal choroidal neovascularization with or without classic CNV secondary to AMD
PrONTO	Prospective Optical coherence tomography imaging of patients with Neovascular AMD Treated with intra-Ocular ranibizumab
TAP	Treatment of Age-related macular degeneration with Photodynamic therapy
VISION	VEGF Inhibition Study In Ocular Neovascularization

AMD = age-related macular degeneration; **CNV** = choroidal neovascularization; **VEGF** = vascular endothelial growth factor.

acuity than if the first eye to be affected were treated (when the unaffected eye compensates for loss of vision in the affected eye). Only two studies included a first-eye model, and in both cases this was evaluated alongside a second-eye model.

The major factors that had an impact on cost effectiveness were the timeframes used in the model, and the inclusion or exclusion of indirect costs of treatment (i.e. societal costs related to blindness, including caregiver costs). The timeframes taken into account by the models ranged from 1 year to a lifetime, and were generally extrapolated from 1–5 years of treatment. The types of wet AMD assessed most frequently were classic or predominantly classic AMD, but many studies included all types of the disease. Table II provides an overview of the methodology of the cost-utility studies included in the review. Treatment of the predominantly classic form of AMD was typically associated with lower incremental cost-effectiveness ratios (ICERs) than treatment of the occult disease form.

2. Comparison of Treatments with Best Supportive Care, Usual Care or Placebo

2.1 Laser Photocoagulation

2.1.1 Cost Utility

Laser photocoagulation was shown to be a cost-effective treatment option for wet AMD in the US in three studies based on data from the MPS group. Costs per QALY gained for laser photocoagulation compared with no treatment or with observation were $US5629–23 176 over time horizons of 11–14 years (table III).[10-12]

2.1.2 Other Cost-Effectiveness Measures

Data from a number of clinical trials, along with allowable Medicare amounts for 2006, were used to determine cost effectiveness of laser photocoagulation in the US by costs per Snellen line-year gained; the cost per Snellen line-year gained for extrafoveal disease was $US77, and for juxtafoveal and subfoveal disease was $US176.[32]

2.2 Photodynamic Therapy with Verteporfin

Before the availability of VEGF inhibitors for the treatment of wet AMD, PDT was the mainstay of therapy, and so its cost effectiveness has been evaluated extensively. Most analyses used efficacy data from the TAP study, a randomized double-masked trial of 609 patients with CNV, which showed that PDT with verteporfin could reduce the risk of vision loss (≥15 letters) over 12 months compared with placebo.[33]

Most studies that modelled time horizons of ≥5 years have shown PDT with verteporfin to be cost effective (<£30 000 or $US50 000–100 000 per QALY gained) compared with usual care, placebo or routine clinical practice in Canada, Switzerland, the UK and the US. Tables III and IV present summaries of the cost-effectiveness outcomes for PDT compared with usual care, no treatment or placebo.

2.2.1 Cost Utility

Using 5-year efficacy data, the estimated cost per QALY gained was <£30 000 in the UK over a 10-year time horizon[14] and <$US50 000 in the US over a 12-year time horizon for predominantly classic/classic AMD.[11,15] A Canadian HTA evaluated PDT from a societal perspective over an 8-year timeframe, and also judged it to be cost effective (<$Can50 000) both for predominantly classic CNV and for classic and occult CNV;[13] however, Sharma et al.[19] evaluated PDT from a third-party payer's perspective using 1- to 2-year TAP data and found PDT to be of poor-to-modest cost effectiveness based on an 11-year timeframe.

PDT was found to be more likely to be cost effective when given early in the course of the disease to patients with better visual acuity; a study using a 7-year evaluation period in an Australian setting[17] and a 5-year period in the UK[20] both showed that PDT was borderline cost effective versus placebo for patients with 'reasonable' initial visual acuity (6/12 [20/40])[1] at treatment

1 The standard definition of normal visual acuity (20/20 or 6/6 vision) is the ability to resolve a spatial pattern separated by a visual angle of 1 minute of arc. A person with a visual acuity of 6/12 (20/40) can resolve the same pattern at a distance of 6 metres (20 feet) as a person with 'normal' visual acuity can at 12 metres (40 feet).

Table II. Summary of the methods of the reviewed cost-utility papers

Study, country, currency, y of values	Perspective (comparator)	No. of tx	Annual disc. rate (%)	Model type
Cost utility of laser photocoagulation vs UC, no tx or PL				
Brown et al.,[10] US, $US, 1999	Third-party payer; 1 y of tx; 11-y timeframe (no tx)	NR	3.0	2nd eye
Brown et al.,[11] US, $US, 2005	Third-party payer – health insurance; 1 y of tx; 12-y timeframe (no tx)	1.5 over 1 y	3.0	2nd eye
Busbee et al.,[12] US, $US, 2001	Third-party payer – health insurance; up to 5 y of tx; 14-y timeframe (observation)	2	3.0	NR
Cost utility of PDT vs verteporfin with UC, no tx or PL				
Larouche and Rochon (AETMIS – HTA),[13] Canada, $Can, NR	Societal; 3 y of tx; 8-y timeframe (no tx)	3.4 in y 1 2.1 in y 2 1 in y 3	3.0	Combined eye
Bansback et al.,[14] UK, £, NR	NR; up to 10 y of tx; 2-, 5- and 10-y timeframes (BSC)	As per TAP[a]	3.5	2nd eye
Brown et al.,[11] US, $US, 2005	Third-party payer – health insurance; 12-y timeframe (no tx)	8.1 over 12 y	3.0	2nd eye
Brown et al.,[15] US, $US, 2004	Third-party payer – health insurance; 12-y timeframe (PL)	8.1 over 12 y	3.0	2nd eye
Donati,[16] Switzerland, €, NR	Healthcare system; societal; 3 y of tx; 3-y timeframe (PL)	3 over 3 y	0.0	NR
Hopley et al.,[17] Australia, $A/£, 2003	Third-party payer; 7 y of tx; 7-y timeframe (PL)	10.9 over 7 y	6.0	2nd eye
Meads et al. (HTA),[18] UK, £, 2001	Health service and societal; 2 y of tx; 2-y timeframe (BSC)	1–8 over 2 y	0.0	2nd eye
Sharma et al.,[19] Canada, $US, NR	Third-party payer; 2- and 11-y timeframes (PL)	5.5 over 2 y	3.0	2nd eye
Smith et al.,[20] UK, £, 2001	Govt and tx costs only; 3 y of tx; 2- and 5-y timeframes (PL)	NR	6.0 (costs); 2.0 (benefits)	2nd eye
Cost utility of PG vs UC, no tx or PL				
Brown et al.,[11] US, $US, 2005	Third-party payer – health insurance; 12 y of tx; 12-y timeframe (no tx)	18.3 over 12 y	3.0	2nd eye
Colquitt et al. (HTA),[2] UK, £, 2005	Healthcare system and Personal Social Services; 2 y of tx; 2- and 10-y timeframes (UC)	9 in y 1 8 in y 2	3.5	NR
Earnshaw et al.,[21] Canada, $Can, 2004	Healthcare system; 2 y of tx; lifetime timeframe (UC)	8.4 in y 1 6.9 in y 2	3.0	2nd eye
Javitt et al.,[22] US, $US, 2006	Third-party payer; 2 y of tx; lifetime timeframe (PG/PDT vs PDT/UC)	8.4 in y 1 6.9 in y 2	3.0	2nd eye
Wolowacz et al.,[23] UK, £, NR	UK Govt; 2 y of tx; 10-y timeframe (BSC)	12.6 over 2 y	3.5	2nd eye
Cost utility of RB vs UC, no tx or PL				
Brown et al.,[24] US, $US, 2006	Third-party payer – health insurance; 2 y of tx; 12-y timeframe (sham tx)	22 over 2 y	3.0	1st, 2nd and combined eye
Colquitt et al. (HTA),[2] UK, £, 2005	Healthcare system and Personal Social Services; 1 y of tx (predominantly classic CNV); 2 y of tx (minimally classic CNV); 1- to 2- and 10-y timeframes (BSC)	12 over 1 y (predominantly classic CNV); 24 over 2 y (minimally classic CNV)	3.5	NR

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Table II. Contd

Study, country, currency, y of values	Perspective (comparator)	No. of tx	Annual disc. rate (%)	Model type
CADTH (CDR – manufacturer's model – HTA),[25] Canada, $Can, 2007	Third-party payer; 1 y of tx [ANCHOR and PIER]; 2 y of tx [MARINA]; 10-y timeframe (BSC)	ANCHOR, PIER or MARINA regimen	5.0	2nd eye
CADTH (CDR – CADTH model[b] – HTA),[25] Canada, $Can, 2007	Third-party payer; 1 y of tx [ANCHOR and PIER]; 2 y of tx [MARINA]; 10-y timeframe (BSC)	ANCHOR, PIER or MARINA regimen	NR	2nd eye
Hurley et al.,[26] US, $US, 2004	Societal; third party – healthcare funder; 4 y of tx; 2- and 10-y timeframes (UC)	12 in y 1 12 in y 2 4 in y 3 4 in y 4	3.0	2nd eye
Neubauer et al.,[27] Germany, €, NR	Societal; 2 y of tx; 10-y timeframe (BSC)	6 per y for 2 y	5.0	2nd eye
Between-treatment comparisons of cost utility				
Brown et al. (HTA),[28] Canada, $Can, NR	Provincial healthcare provider – direct costs only; 2 y of tx; life expectancy timeframe (PDT vs PG; RB vs PG)	PDT: 2 per y PG: 8 per y RB: 12 per y	5.0	2nd eye
Colquitt et al. (HTA),[2] UK, £, 2005	Healthcare system and Personal Social Services; 1 y of tx; 1- to 2- and 10-y timeframes (RB vs PDT)	RB: 12 over 1 y PDT: average no. reported in ANCHOR	3.5	NR
CADTH (CDR – manufacturer's model – HTA),[25] Canada, $Can, 2007	NR; 1 y of tx (RB vs PDT)	RB and PDT: ANCHOR regimen	5.0	2nd eye
CADTH (CDR – CADTH model[b] – HTA),[25] Canada, $Can, 2007	NR; 1 y of tx; timeframe NR (RB vs PDT)	RB and PDT: ANCHOR regimen	5.0	2nd eye
Earnshaw et al.,[21] Canada, $Can, 2004	Healthcare system; 2 y of tx; lifetime timeframe (PG vs PDT)	PG: 8.4 in y 1 6.9 in y 2 PDT: 3.4 in y 1 2.2 in y 2	3.0	2nd eye
Fletcher et al.,[29] US, $US, NR	Third-party payer; 2 y of tx; 2-y timeframe (RB vs BSC; PG vs BSC; PDT vs BSC)	RB: (i) 12 in y 1; 12 in y 2;[c] (ii) 6 in y 1; 4 in y 2;[d] PG: 8.4 in y 1; 6.9 in y 2; PDT: 3.4 in y 1; 2.2 in y 2	3.0	1st and 2nd eye
Hernandez-Pastor et al.,[30] Spain, €, 2007	Third-party payer; 2-y and lifetime tx; 2-y and life expectancy timeframes (RB vs PDT)	RB: 12 per y PDT: 2.8 in y 1 1 per y thereafter	3.0	2nd eye
Hernandez-Pastor et al.,[31] Spain, €, 2008	Societal; lifetime tx; life expectancy timeframe (RB vs PG)	RB: 12 per y PG: 8 per y	3.5	2nd eye

a See table I for definitions of study acronyms.

b Assuming the Product Listing Agreement is implemented. In this agreement, the manufacturer covers the cost of ranibizumab if the patient requires more than nine vials in year 1 or six vials in years 2 and 3 of tx.

c MARINA regimen.

d PIER regimen.

$A = Australian dollars; **AETMIS** = Agence D'évaluation Des Technologies Et Des Modes D'intervention En Santé; **BSC** = best supportive care; **CADTH** = Canadian Agency for Drugs and Technologies in Health; **CDR** = Common Drug Review; **CNV** = choroidal neovascularization; **disc.** = discount; **Govt** = government; **HTA** = health technology assessment; **NR** = not reported; **PDT** = photodynamic therapy; **PG** = pegaptanib; **PL** = placebo; **RB** = ranibizumab; **tx** = treatment(s); **UC** = usual care.

Table III. Summary of the results of the cost-utility analyses[a]

Study, currency[b]	Cost		QALYs gained		ICER (cost per QALY gained)
	intervention	comparator	intervention	comparator	
Laser photocoagulation vs UC, no tx or PL					
Brown et al.,[10] $US	NR		0.186		5629
Brown et al.,[11] $US	2012		0.246		8179
Busbee et al.,[12] $US	1715		0.0740		23176
Cost utility of PDT vs verteporfin with UC, no tx or PL					
Larouche and Rochon (AETMIS – HTA),[13] $Can					
Predominantly classic CNV	664085	494112	49	44	33880
Classic and occult CNV	664085	494112	49	44	43253
Bansback et al.,[14] £	9381	3491	0.773	0.702	82329 (2y)
	15041	9500	1.668	1.503	33710 (5y)
	21246	16600	2.550	2.329	20996 (10y)
Brown et al.,[11] $US	15488		0.491		31544
Brown et al.,[15] $US	15277		0.491		31013
Donati,[16] €	26400	19494	0.106		65150
Hopley et al.,[17] $A/£					
Initial visual acuity 6/12 (20/40)	12478		0.395		31607
Initial visual acuity 6/60 (20/200)	12478		0.197		63214
Meads et al. (HTA),[18] £	5658		0.0311		182188 (1y of blindness)
	4695		0.0311		151179 (2y of blindness)
Sharma et al.,[19] $US					
Initial visual acuity 6/12 (20/40)			NR		2y, 86721 11y, 43547
Initial visual acuity 6/60 (20/200)					2y, 173984 11y, 87197
Smith et al.,[20] £					
Government perspective					
Visual acuity 6/12 (20/40)	6490	1275	1.205	1.136	75580 (2y)
	11700	10200	2.375	2.205	8823 (5y)

Continued next page

Table III. Contd

Study, currency[b]	Cost		QALYs gained		ICER (cost per QALY gained)
	intervention	comparator	intervention	comparator	
Visual acuity 6/30 (20/100)	8 878	4 590	0.995	0.980	285 867 (2 y)
	18 500	15 700	2.093	1.999	29 787 (5 y)
Tx costs-only perspective					
Visual acuity 6/12 (20/40)	6 173	0	1.205	1.136	89 464 (2 y)
	6 475	0	2.375	2.205	38 088 (5 y)
Visual acuity 6/30 (20/100)	6 173	0	0.995	0.980	411 533 (2 y)
	6 475	0	2.093	1.999	68 882 (5 y)
Cost utility of PG vs UC, no tx or PL					
Brown et al.,[11] $US	24 314		0.363		66 978
Colquitt et al. (HTA),[2] £	12 817	2 558	1.43	1.37	163 603 (2 y)
	24 662	16 600	4.15	3.89	30 986 (10 y)
Earnshaw et al.,[21] $Can	20 016	UC, 7669	4.17	UC, 3.96	59 039
Javitt et al.,[22] $US					
Early subfoveal CNV	66 638	55 108	4.75	4.44	36 282
Moderate subfoveal CNV	84 185	71 393	3.59	3.38	58 280
Late subfoveal CNV	96 771	84 400	2.86	2.77	132 381
Wolowacz et al.,[23] £	28 494	26 111	3.324	3.027	8 023
Cost utility of RB vs UC, no tx or PL					
Brown et al.,[24] $US	52 652		2nd-eye model, 1.039 1st-eye model, 0.425 Combined-eye model, 0.710		2nd-eye model, 50 691 1st-eye model, 123 887 Combined-eye model, 74 169
Colquitt et al. (HTA),[2] £					
Predominantly classic CNV	12 427	933	0.81	0.74	160 181 (1–2 y)
	26 888	20 431	4.15	3.59	11 412 (10 y)
Minimally classic CNV or occult CNV with no classic lesions	23 902	1 541	1.54	1.40	152 464 (1–2 y)
	31 096	13 787	4.79	4.10	25 098 (10 y)
CADTH (CDR – manufacturer's model – HTA),[25] $Can					
Predominantly classic CNV	79 512	74 058	5.37	5.12	21 857 (ANCHOR regimen)
	75 875	72 720	5.01	4.77	12 871 (PIER regimen)
Minimally classic CNV	73 158	60 445	4.48	3.14	9 542
Occult with no classic CNV	64 864	51 158	5.93	5.57	10 345

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Table III. Contd

Study, currency[b]	Cost		QALYs gained		ICER (cost per QALY gained)
	intervention	comparator	intervention	comparator	
CADTH (CDR, CADTH model[c] – HTA),[25] $Can	Modified version of manufacturer's model				
Predominantly classic CNV					26 619 (ANCHOR regimen)
					21 148 (PIER regimen)
Minimally classic CNV					48 917
Occult with no classic CNV					52 678
Hurley et al.,[26] $US					
Including caregiver costs	78 900	42 700	0.118		308 400 (2 y)
	205 800	238 300	0.68		Dominant (10 y)
Excluding caregiver costs	56 700	5 800	0.118		432 900 (2 y)
	88 800	26 300	0.68		91 900 (10 y)
Neubauer et al.,[27] €					
Predominantly classic CNV	6 697		0.40		16 882
Minimally classic CNV	8 010		0.32		24 766
Occult CNV	8 826		0.34		26 170
Between-treatment comparisons of cost utility					
Brown et al. (HTA),[28] $Can	102 472	96 975	5.60	5.98	PG is dominant
Predominantly classic CNV	140 706	96 975	6.75	5.98	56 382
Any CNV lesion	138 733	97 569	6.72	5.98	56 194
Colquitt et al. (HTA),[2] £	12 427	4 182	0.81	0.77	202 450 (1–2 y)
	26 888	21 498	4.15	3.81	15 638 (10 y)
CADTH (CDR – manufacturer's model – HTA),[25] $Can	79 512	78 666	5.37	5.17	4 167
CADTH (CDR – CADTH model[c] – HTA),[25] $Can	NR	NR	NR	NR	5 191
Earnshaw et al.,[21] $Can	20 016	15 345	4.17	3.87	49 052
Fletcher et al.,[29] $US			NR		992 103 (MARINA regimen) [RB vs BSC]
			NR		626 938 (PIER regimen) [RB vs BSC]
			NR		1 483 973 (PG vs BSC)
			NR		986 913 (PDT vs BSC)
Hernandez-Pastor et al.,[30] €	31 265	12 937	1.143	1.003	1 312 752 (2 y)
	163 588	49 721	7.412	4.522	39 398 (lifetime)
Hernandez-Pastor et al.,[31] €	164 870	93 664	6.911	4.474	29 224

a See table I for definitions of study acronyms.

b See table II for details regarding the methods for each study including the year of value.

c Assuming the Product Listing Agreement is implemented. In this agreement, the manufacturer covers the cost of ranibizumab if the patient requires more than nine vials in year 1 or six vials in years 2 and 3 of tx.

$A = Australian dollars; **AETMIS** = Agence D'évaluation Des Technologies Et Des Modes D'intervention En Santé; **BSC** = best supportive care; **CADTH** = Canadian Agency for Drugs and Technologies in Health; **CDR** = Common Drug Review; **CNV** = choroidal neovascularization; **HTA** = health technology assessment; **ICER** = incremental cost-effectiveness ratio; **NR** = not reported; **PDT** = photodynamic therapy; **PG** = pegaptanib; **PL** = placebo; **RB** = ranibizumab; **tx** = treatment; **UC** = usual care.

Table IV. Summary of the methods and results of economic evaluations using other cost-effectiveness measures[a]

Study, country, currency, y of pricing	Perspective (comparator)	No. of tx	Annual disc. rate (%)	Model type	Outcome measures and results
PDT and verteporfin vs UC, no tx or PL					
Donati,[16] Switzerland, €, NR	Healthcare system; societal; 3 y of tx; 3-y timeframe (PL)	3 over 3 y	0.0	NR	PDT: cost per vision-y gained ranged from 8239 to 10 271 ICER ranged from 3846 to 7416
Greiner,[34] Switzerland, SwF, 1998	Societal; 6 tx in 3 y; 3-y timeframe (PL)	3 in y 1 2 in y 2 1 in y 3	NR	NR	PDT: cost 15 921; vision-y saved 1.068; cost per vision-y 14 907 PL: cost 10 397; vision-y saved 0.494; cost per vision-y 21 047 ICER 9624
MSAC (HTA – data from sponsor)[35] Australia, $A, NR	Societal; 2 y of tx; timeframe NR (PL)	NR	NR	NR	Incremental cost 14 038 Incremental vision-y gained 0.0396 ICER 35 346
Muslera and Natal,[36] Spain, €, NR	Healthcare system; 2-y and lifetime timeframes (no tx)	Median 5 tx over 2 y	2.5	NR	*Quality-adjusted cost per visual-acuity life-y gained* Visual acuity maintained for 2 y: women 70 249; men 66 931 Visual acuity maintained for a lifetime: women (17 y) 7794; men (13 y) 9743
Smiddy,[32] US, $US, 2006	Third-party payer; 1 y of tx; lifetime timeframe (no tx)	3.4 in y 1	NR	NR	*Predominantly or minimally classic CNV* Snellen lines saved 1.44; cost per Snellen line-y 448 *Occult CNV* Snellen lines saved 1.17; cost per Snellen line-y 551
Smith et al.,[20] UK, £, 2001	Govt and tx costs only; 3 y of tx; 2- and 5-y timeframes (PL)	NR	6.0 (costs); 2.0 (benefits)	2nd eye	*Incremental cost per vision-y gained* Govt perspective – visual acuity 6/12 (20/40) 2 y 33 645; 5 y 1685 Govt perspective – visual acuity 6/30 (20/100) 2 y 13 877; 5 y 4402 Tx costs only – visual acuity 6/12 (20/40) 2 y 39 826; 5 y 7275 Tx costs only – visual acuity 6/30 (20/100) 2 y 19 977; 5 y 10 180
PG vs UC, no tx or PL					
Earnshaw et al.,[21] Canada, $Can, 2004	Healthcare system; 2 y of tx; lifetime timeframe (UC)	8.4 in y 1 6.9 in y 2	3	2nd eye	Cost: PG 20 016; UC 7669; PL 6737 Vision-y gained: PG 3.83; UC 3.26; PL 2.62 Cost per vision-y gained: 21 559

Continued next page

Table IV. Contd

Study, country, currency, y of pricing	Perspective (comparator)	No. of tx	Annual disc. rate (%)	Model type	Outcome measures and results
Javitt et al.,[22] [a] US, $US, 2006	Third-party payer; 2 y of tx; lifetime timeframe (UC)	8.4 in y 1 6.9 in y 2	3	2nd eye	*Early subfoveal CNV* PG: cost 66 638; vision-y gained 5.26 UC: 55 108; vision-y gained 4.50 ICER 15 279 *Moderate subfoveal CNV* PG: cost 84 185; vision-y gained 3.75 UC: 71 393; vision-y gained 3.12 ICER 20 350 *Late subfoveal CNV* PG: cost 96 771; vision-y gained 0.42 UC: 84 400; vision-y gained 0.21 ICER 57 230
Smiddy,[32] US, $US, 2006	Third-party payer; 1 y of tx; lifetime timeframe (no tx)	8.3 in y 1	NR	NR	Cost per Snellen line 12 482 Snellen lines saved 1.04 Cost per Snellen line-y 1248
Wolowacz et al.,[23] UK, £, NR	UK Govt; 2 y of tx; 10-y timeframe (BSC)	12.6 over 2 y	3.5	2nd eye	PG: cost 28 494; vision-y gained 3.177 BSC: cost 26 111, vision-y gained 2.293
RB vs UC, no tx or PL					
Cohen et al.,[37] France, €, 2006	Societal; 1 y of tx; 1-y timeframe (UC)	8 over 1 y	NR	NR	*Improvement in visual acuity (>15 letters on ETDRS scale)* RB: cost 9123; success rate 0.488; cost per success 18 721 UC: cost 7604; success rate 0.339; cost per success 22 543 *Legal blindness avoided* RB: cost 9196; success rate 0.997; cost per success 9224 UC: cost 5713; success rate 0.931; cost per success 6133
Colquitt et al. (HTA),[2] UK, £, 2005	Healthcare system and Personal Social Services; 1 y of tx (predominantly classic CNV); 2 y of tx (minimally classic CNV); 1- to 2- and 10-y timeframes (BSC)	12 over 1 y (predominantly classic CNV); 24 over 2 y (minimally classic CNV)	3.5	NR	*Predominantly classic CNV* RB: 1- to 2-y costs 12 427; vision-y saved 0.98 RB: 10-y costs 26 888; vision-y saved 3.59 BSC: 1- to 2-y costs 933; vision-y saved 0.85 BSC: 10-y costs 20 431; vision-y saved 2.28 *Minimally classic or occult with no classic lesions CNV* RB: 1- to 2-y costs 23 902; vision-y saved 1.87 RB: 10-y costs 31 096; vision-y saved 5.19 BSC: 1- to 2-y costs 1541; vision-y saved 1.64 BSC: 10-y costs 13 787; vision-y saved 3.78

Continued next page

Table IV. Contd

Study, country, currency, y of pricing	Perspective (comparator)	No. of tx	Annual disc. rate (%)	Model type	Outcome measures and results
Hurley et al.,[26] US, $US, 2004	Societal; third party – healthcare funder; 4 y of tx; 2- and 10-y timeframes (UC)	12 in y 1 12 in y 2 4 in y 3 4 in y 4	3.0	2nd eye	*Incremental cost per case of blindness prevented* Including caregiver costs: 2 y 145 400; 10 y dominant Excluding caregiver costs: 2 y 204 100; 10 y, 217 700 *Incremental cost per blind-y prevented* Including caregiver costs: 2 y 116 500; 10 y dominant Excluding caregiver costs: 2 y 163 500; 10 y 29 200
CADTH (CDR – manufacturer's model – HTA),[25] Canada, $Can, 2007	Third-party payer; 1 y of tx (ANCHOR and PIER); 2 y of tx (MARINA); 10-y timeframe (BSC)	ANCHOR, PIER or MARINA regimen	5.0	2nd eye	*Predominantly classic CNV* ANCHOR regimen: vision-y gained 2.86 for RB vs 1.81 for BSC; ICER 5238 PIER regimen: vision-y gained 2.68 for RB vs 1.93 for BSC; ICER 4166 *Minimally classic CNV* Vision-y gained 4.48 for RB vs 3.14 for BSC; ICER 9542 *Occult with no classic CNV* Vision-y gained 5.33 for RB vs 4.00 for BSC; ICER 10 345

					Regimen	***Cost of tx***	***Snellen lines saved***	***Cost per Snellen line-y of life expectancy***
Smiddy,[38] US, $US, NR	Third-party insurer; 2 y of tx; 10-y timeframe (no tx)	22.4 over 2 y	NR	NR	ANCHOR	NR	6.2 6.6	474 (1 y) 827 (2 y)
		22.4 over 2 y	NR	NR	MARINA	NR	3.5 4.3	766 (1 y) 1532 (2 y)
		6 over 1 y or 10 over 2 y	NR	NR	PIER	16 170 26 880	3.2 3.8	505 (1 y) 707 (2 y)
		5.6 over 1 y or 9.9 over 2 y	NR	NR	PrONTO	15 472 21 499	4.4 4.5	344 (1 y) 611 (2 y)

a See table I for study acronyms.

b PG/PDT vs PDT/UC.

$A = Australian dollars; **BSC** = best supportive care; **CADTH** = Canadian Agency for Drugs and Technologies in Health; **CDR** = Common Drug Review; **CNV** = choroidal neovascularization; **disc.** = discount; **Govt** = government; **HTA** = health technology assessment; **ICER** = incremental cost-effectiveness ratio; **MSAC** = Medical Services Advisory Committee; **NR** = not reported; **PDT** = photodynamic therapy; **PG** = pegaptanib; **PL** = placebo; **RB** = ranibizumab; **tx** = treatment(s); **SwF** = Swiss franc; **UC** = usual care.

initiation, but was not cost effective for patients with 'poor' initial visual acuity (6/60 [20/200] in the Australian analysis, 6/30 [20/100] in the UK analysis). In the UK analysis, PDT was shown to be cost effective for patients with 'poor' initial visual acuity when indirect costs were included.[20]

Over shorter timeframes (2–3 years), PDT was not generally shown to be cost effective compared with best supportive care, as demonstrated by studies in the UK[18] and Switzerland.[16] Similarly, studies that found PDT to be cost effective over ≥5 years yielded ICERs considerably above accepted cost-effectiveness thresholds when time horizons of 1–2 years were considered.[14,19,20]

2.2.2 Other Cost-Effectiveness Measures

Annual costs for maintaining vision over the duration of life expectancy were found to be €7794 per vision-year gained for women (17-year life expectancy) and €9743 for men (13-year life expectancy) in Spain.[36] Data from several clinical trials, along with allowable Medicare amounts for 2006, were used to determine the cost effectiveness of PDT in the US; costs per Snellen line-year gained were $US448 for predominantly or minimally classic CNV and $US551 for occult CNV.[32]

In Switzerland, two studies evaluated cost effectiveness in terms of vision-years gained and calculated costs of €8239–10 271 and Swiss franc (SwF)9624 per vision-year gained over a 3-year timeframe.[16,34]

2.3 Pegaptanib

Pegaptanib is a pegylated, modified oligonucleotide that binds to and inhibits VEGF-A. Most studies that evaluated pegaptanib used data from the VISION study. VISION demonstrated the ability of pegaptanib to stabilize the visual acuity of patients with wet AMD.[7] Summaries of cost-effectiveness analyses of pegaptanib are presented in tables III and IV.

2.3.1 Cost Utility

A UK-based analysis by Wolowacz et al.[23] showed treatment with pegaptanib to be cost effective relative to best supportive care for subfoveal wet AMD over a 10-year timeframe from a governmental perspective; ICERs were lower when visual acuity at treatment initiation was better. However, an HTA by Colquitt et al.[2] calculated higher costs per QALY gained over the same timeframe and from a similar perspective.

A Canadian study[21] showed pegaptanib to be 'moderately' cost effective ($Can20 000–100 000 per QALY gained) compared with usual care when modelled using VISION efficacy data and a lifetime timeframe.

In the US, Brown et al.[11] showed that pegaptanib treatment of classic subfoveal CNV was 'moderately' cost effective (cost per QALY gained $US50 000–100 000) compared with no treatment over 12 years. Javitt et al.[22] found pegaptanib to be cost effective compared with usual care only when treatment was initiated in the early or moderate stages of disease.

2.3.2 Other Cost-Effectiveness Measures

Data from a number of clinical trials, along with allowable Medicare amounts for 2006, were used to determine cost effectiveness of pegaptanib in the US: cost per Snellen line-year gained was $US1248.[32] Incremental costs per vision-year gained varied widely, ranging from £2696 from a governmental perspective in the UK[23] for all types of wet AMD, to $US57 230 from a third-party payer perspective (for late subfoveal CNV).[22]

2.4 Ranibizumab

Ranibizumab is a humanized recombinant monoclonal antibody fragment directed against VEGF-A. Ranibizumab inhibits VEGF-A, thereby preventing endothelial cell proliferation and neovascularization, and slowing progression of wet AMD. In addition to stabilizing wet AMD, ranibizumab can significantly improve vision: in two pivotal randomized controlled trials (RCTs),[8,9] more than 30% of patients with minimally classic lesions treated monthly with ranibizumab 0.5 mg, and more than 40% of patients with predominantly classic lesions treated monthly with ranibizumab 0.5 mg plus PDT, gained ≥15 letters on the ETDRS chart within 12 months; this compared with approximately 5% of those who received sham treatment or sham plus PDT, respectively. Tables III

and IV summarize the cost-effectiveness outcomes for ranibizumab compared with usual care, no treatment or placebo.

2.4.1 Cost Utility

Ranibizumab was found to be cost effective in Canada, Germany, the UK and the US when outcomes were viewed over a long-term time horizon (>10 years). Ranibizumab was also recommended by HTAs in Argentina,[39] Australia[40] and Scotland[41] based on their review of the available economic evidence. Most of the studies that assessed cost effectiveness of ranibizumab used data from the MARINA[9] and ANCHOR[8] studies, where intraocular injections were given on a monthly basis. However, some studies also investigated alternative regimens, such as the PIER[42] or PrONTO regimens,[43] where ranibizumab was administered less frequently. Notably, HTAs from the UK[2,41] reported results from the manufacturer's cost-effectiveness model, which applied a dosing regimen of eight injections in the first year and six injections in subsequent years, different from those used in the MARINA and ANCHOR clinical trials. Importantly, the PrONTO study subsequently showed that less frequent dosing was effective in the majority of patients; ranibizumab was administered once monthly for 3 months and then as needed, and a mean of 5.6 injections was administered per patient over 12 months.[44]

In Germany, Neubauer et al.[27] modelled cost effectiveness from a societal perspective using visual acuity data from the MARINA and ANCHOR clinical studies. Cost effectiveness was determined separately for the three different fluorescein angiographic subtypes of AMD included in the clinical studies, and ranibizumab was associated with a cost per QALY gained of <€30 000 for each subtype.[27]

Data from the MARINA study were also used to model cost effectiveness for minimally classic/occult CNV in a US setting,[24,26] and ranibizumab was shown to be 'moderately' cost effective from a third-party healthcare provider perspective over a ≥10-year timeframe. Moreover, in the analysis by Hurley et al.,[26] ranibizumab was found to be cost saving compared with usual care in the US when caregiver costs were taken into account.

The Canadian Agency for Drugs and Technologies in Health (CADTH)[25] conducted an independent economic evaluation of the manufacturer's cost-effectiveness data and concluded that ranibizumab treatment was cost effective compared with best supportive care if the Product Listing Agreement (where the manufacturer pays for additional treatments if patients require more than nine injections in the first year or more than six injections in the second and third years) was implemented.

The cost effectiveness (cost per QALY gained of <£30 000) of ranibizumab was also demonstrated by an HTA in the UK for both predominantly classic CNV (data from the ANCHOR trial) and minimally classic/occult CNV (data from the MARINA trial) when costs and benefits, including cost of blindness, were considered over a 10-year timeframe.[2] A probabilistic sensitivity analysis showed that, for patients with predominantly classic lesions, ranibizumab had a probability of being cost effective (compared with best supportive care) of 95% at a willingness-to-pay (WTP) threshold of £20 000 per QALY gained and 99% at a WTP threshold of £30 000 per QALY gained.

2.4.2 Other Cost-Effectiveness Measures

Five studies have evaluated the cost effectiveness of ranibizumab using measures other than QALYs. In France, it was concluded that ranibizumab was cost effective compared with usual care when assessed by improvements in visual acuity modelled over 1 year. The simulation used efficacy data from a number of published clinical studies and allowed patients to switch treatments if they were ineffective. Ranibizumab also reduced the rate of legal blindness, although costs per success for this endpoint were higher than with usual care.[37] By contrast, Hurley et al.[26] found ranibizumab to be cost saving compared with usual care over a 10-year time horizon, when evaluated by cases of blindness prevented and blind-years prevented, and viewed from a societal perspective in the US. HTAs in the UK and Canada found 2 years of monthly ranibizumab injections to be associated with incremental costs per vision-year saved of £12 275 and $Can9542,

respectively, for minimally classic or occult with no classic CNV, over a 10-year timeframe; incremental costs for predominantly classic CNV were £4929 and $Can5238, based on 1 and 2 years of ranibizumab treatment, respectively.[2,25]

Costs per Snellen line-year of life-expectancy were found to be $US827, $US1532 and $US707 for the ANCHOR, MARINA and PIER regimens of ranibizumab treatment, respectively, assuming 2 years of treatment and a 10-year timeframe.[38] Another alternative ranibizumab regimen used in the PrONTO study, where injections were given as needed, was also evaluated and found to cost $US611 per Snellen line-year of life-expectancy.

3. Comparison of Treatment Options

Studies that compared more than one treatment option for wet AMD are presented in table III. In a UK-based HTA, ranibizumab was shown to be cost effective compared with PDT for predominantly classic CNV (data from the ANCHOR trial) over a 10-year time horizon.[2] The CADTH also showed that ranibizumab was cost effective compared with pegaptinib, based on 1 year of treatment; cost per QALY gained with ranibizumab was approximately $Can50 000; that is, at the commonly accepted cost-effectiveness threshold.[28]

Ranibizumab was cost effective (<€30 000 per QALY gained) compared with pegaptanib for minimally classic disease from a societal perspective in a Spanish setting.[30,31] From a third-party payer's perspective, ranibizumab treatment was slightly above the generally accepted cost-effectiveness threshold when administered according to the ANCHOR regimen; however, sensitivity analysis showed that it had a lower cost per QALY gained (<€5000), well below the cost-effectiveness threshold, when administered as needed.

Pegaptanib was a cost-effective treatment alternative to PDT for subfoveal wet AMD in Canada when costs related to wet AMD comorbidities were taken into consideration.[21] In a US study of patients with classic subfoveal CNV,[11] laser photocoagulation was associated with a lower cost per QALY ($US8179) than PDT ($US31 544) and pegaptanib ($US66 978). PDT and pegaptanib improved quality of life (QOL) to a greater extent; compared with no treatment, PDT could be considered cost effective (ICER <$US50 000 per QALY gained) and pegaptanib treatment could be considered 'moderately' cost effective ($USUS50 000–100 000 per QALY gained).

In the US,[29] a decision-tree analysis using a 2-year timeframe and a variety of published trial data for the cost effectiveness of individual wet AMD therapies relative to best supportive care showed that ranibizumab was associated with a lower average cost per QALY than pegaptanib and PDT when administered using the PIER regimen (table III). When using the MARINA regimen, ranibizumab had a lower ICER than pegaptanib and a similar ICER to PDT; however, because of the 2-year time horizon employed, none of the treatments analysed met the generally accepted threshold for cost effectiveness ($US50 000–100 000 per QALY gained). An exploratory analysis over 5 years showed the importance of time horizon, in that the cost per QALY gained for best supportive care rose markedly as the proportion of blindness and related costs increased, whereas the cost per QALY gained (and hence ICER compared with best supportive care) for ranibizumab, pegaptanib and PDT fell compared with the 2-year assessment.

4. Bevacizumab

Bevacizumab is an anti-VEGF-A antibody licensed for the treatment of a number of cancers, including metastatic colorectal cancer, non-squamous non-small-cell lung cancer and metastatic breast cancer. Bevacizumab is not licensed for the treatment of wet AMD; however, because its target is the same as ranibizumab and it has a lower cost once compounded into multiple divided doses from its original oncological dose, it has been used 'off-label' by many physicians.[45,46]

4.1 Cost Utility

There is limited information for evaluating the cost effectiveness of bevacizumab in wet AMD. Bevacizumab is often assumed to be more cost effective than ranibizumab by virtue of its lower unit cost, but to date, health economic studies

have not compared the two treatments directly. As a consequence of the paucity of robust bevacizumab clinical data, our review identified no studies that directly compared the cost utility of bevacizumab with any other treatment for wet AMD. HTAs[28,39] that discussed bevacizumab concluded that there was insufficient evidence to judge its suitability for the treatment of wet AMD. Fletcher et al.[29] evaluated the available data for bevacizumab and estimated a cost per QALY gained of $US104 748 compared with best supportive care (the lowest ICER of all comparators assessed); however, they did not directly compare the cost effectiveness of bevacizumab with other wet AMD therapies because only short-term efficacy data were available and these were not from an RCT. The lack of robust comparative RCT data for bevacizumab was also a major limitation for an exploratory analysis by Raftery et al.[47] This study projected the cost effectiveness of bevacizumab relative to ranibizumab for a range of relative efficacies and determined that, at the current prices, ranibizumab would have to provide 2.5-fold greater efficacy than bevacizumab to be considered cost effective at the generally accepted threshold of £30 000 per QALY gained. However, the model used a rather low cost for bevacizumab (£26 per injection) and by assuming that the adverse effect profiles of ranibizumab and bevacizumab were equal, did not take into account the potential for differences in systemic adverse events that could affect the relative cost-effectiveness ratios of these agents.

4.2 Other Cost-Effectiveness Measures

Smiddy[38] used data from several open-label, non-randomized, uncontrolled treatment studies and calculated a cost per Snellen line-year of $US84–107, depending on whether bevacizumab was administered every 6 weeks, or given as needed.

4.3 Important Considerations for Intraocular Bevacizumab Use

Off-label use of bevacizumab is controversial because there is currently little evidence by which to evaluate its efficacy and long-term safety in the treatment of wet AMD or other retinal diseases. Although the recently completed ABC trial has provided evidence that long-term intravitreal bevacizumab provides visual acuity improvements superior to standard care for wet AMD (pegaptanib or PDT) with a low rate of serious ocular adverse events,[48] there is still relatively little evidence from robust RCTs – the gold standard for evaluating the efficacy and safety of investigational therapies. A recent systematic review[49] of bevacizumab in the treatment of ocular neovascular diseases identified 474 studies, of which nine were RCTs that employed the minimum methodological rigour necessary to generate robust data. Furthermore, methodological flaws within these trials, including potential performance bias in six of the studies and detection bias in five of the studies, precluded any definitive conclusions regarding the safety of intraocular bevacizumab administration. This lack of safety data makes it difficult at present to assess the true cost effectiveness of bevacizumab in wet AMD, at least until the large, ongoing head-to-head studies report their findings (expected in 2011–12[50]).

Differences between the bevacizumab and ranibizumab molecules, and their respective formulations, could affect the safety, efficacy and costs of treatment.[51] Unlike ranibizumab, bevacizumab was not designed for use in the eye, and there is a lack of safety data regarding its intraocular use. Ranibizumab is also formulated to optimize delivery of the active treatment, while avoiding potential ocular and systemic complications. By contrast, bevacizumab is not available at the small doses needed for intravitreal injection, and so vials need to be split for use in AMD if any cost savings are to be made. Splitting vials in this way may lead to problems maintaining sterility and potency (as there are no preservatives in the bevacizumab preparation). There is also a risk that bevacizumab may contain particulate matter that could damage the eye, as it is not manufactured for this use; this is particularly possible if vials have been repackaged by compounding pharmacies.[52] Finally, the pharmacokinetics and pharmacodynamics of bevacizumab are different from those of ranibizumab; bevacizumab binds more weakly to the VEGF-A protein, and is a much larger molecule than rani-

bizumab (149 kDa compared with 48 kDa) with poorer penetration through the retinal layers.[53] Animal studies have shown systemic drug exposure to be greater with bevacizumab than ranibizumab, and so concerns have been raised over the risk of arterio-thromboembolic events.[54-56]

Recently, the French health products safety agency (AFSSAPS) published an information sheet[57] recommending caution in the off-label use of bevacizumab: it highlighted the lack of safety data on the use of bevacizumab in ophthalmology and notes under-notification of adverse effects with the drug. Ocular inflammation, acute vision loss, and tearing or detachment of the retinal pigment epithelium are known risks,[58] and physicians face greater legal responsibility when prescribing outside a drug licence.[59,60]

5. Other Treatments and Treatment Combinations

Screening for early AMD and subsequent prophylactic treatment with zinc and antioxidants was found to be cost effective for delaying and reducing progression of early AMD in Australia.[61] If savings from the reduced need for PDT were included in the model, costs per QALY gained would be lower. The model assumed optician-based screening to identify the number of people with early AMD; outcomes were modelled using data from AREDS. A US study also found prophylactic zinc and antioxidants to be cost effective for patients diagnosed with AMD as assessed by costs per QALY gained;[62,63] Smiddy[32] calculated costs per Snellen line-year at $US473 for vitamin therapy.

Smiddy[32,38] also evaluated the cost effectiveness of various treatment combinations in the US using data from various clinical trials, and allowable Medicare amounts for 2006 or 2008. Triple therapy with PDT plus corticosteroids plus an anti-VEGF-A therapy was associated with an average cost per Snellen line-year of $US71; combinations of PDT with intravitreal triamcinolone or bevacizumab were, on average, slightly more costly at $US66–269 per Snellen line-year, depending on how many treatment cycles were assumed, and what estimates for efficacy were used; and combination of PDT with ranibizumab was calculated at an average of $US355–6195 per Snellen line-year, depending on whether treatment was for 1 or 2 years and whether ranibizumab was administered on a fixed schedule or given as needed.

6. Health Technology Assessments

Recommendations of formal HTAs consistently demonstrate that ranibizumab is currently a cost-effective treatment option for the prevention of vision loss in wet AMD (table V). Seven HTAs conducted since 2007 have evaluated ranibizumab, only one of which did not recommend ranibizumab treatment as being cost effective; this was an assessment in Sweden that did not include a primary economic analysis and concluded that the existing literature on cost effectiveness was insufficient.[64] Of the remaining six, two (from Scotland and Argentina) were essentially unrestricted recommendations.[39,41] The remainder recommended use of ranibizumab with conditions to reduce the overall budget impact; three (from Canada and the UK) recommended a cap on the number of reimbursed doses,[2,25,28] and one (from Australia) recommended limitations on patient subset and prescribing authority.[40] Conditions set on reimbursement allowances were based on assumptions regarding the number of treatments patients would need and the costs of each treatment. In the UK, the cap was placed at 14 ranibizumab injections, mostly because the majority of injections were assumed to be administered as surgical day cases rather than outpatient procedures, thus inflating the costs and pushing cost effectiveness over the ICER threshold.[2] In reality, most ranibizumab injections can be carried out in an outpatient setting or in private ophthalmology rooms, thus making treatment more cost effective than the HTA determined. As noted previously, the PrONTO trial subsequently showed that ranibizumab was effective under a different treatment regimen involving fewer doses on average than the regimen assessed in the UK HTA. All of the HTAs compared ranibizumab with PDT plus verteporfin; the assessments in the UK, Canada and Argentina also concluded that ranibizumab had superior cost effectiveness to pegaptanib.[2,28,39] In addition to these appraisals,

Table V. Health technology assessments (HTAs) of treatments (tx) for wet age-related macular degeneration (AMD)

Reference, country, y	HTA body	Treatments evaluated	Original health economic analysis?	Recommendation
Brown et al.,[28] Canada, 2008	Canadian Agency for Drugs and Technologies in Health	Ranibizumab Pegaptanib PDT with verteporfin Bevacizumab	Yes	**Ranibizumab recommended with dose cap** Ranibizumab is recommended over pegaptanib or PDT as it demonstrates a reversal of the degenerative process in wet AMD. However, a reduction in list price or dosing frequency is required to be cost effective at a WTP of $US50 000 per QALY gained; there is limited clinical trial evidence on the efficacy and safety of bevacizumab in the tx of AMD
Colquitt et al.,[2] UK, 2008	National Institute for Health and Clinical Excellence	Ranibizumab Pegaptanib PDT with verteporfin	Yes	**Ranibizumab recommended with dose cap** Ranibizumab, within its marketing authorization, is recommended as an option for the tx of wet AMD up to the cost of 14 injections in the treated eye and with specific diagnostic criteria; pegaptanib is not recommended for the tx of wet AMD
CDR,[25] Canada, 2008	Canadian Expert Drug Advisory Committee	Ranibizumab PDT with verteporfin	Yes	**Ranibizumab recommended with dose cap** Ranibizumab is recommended for the tx of wet AMD when drug plan coverage is limited to a maximum of 15 vials per pt used to treat the better seeing affected eye
SBU,[64] Sweden, 2008	SBU	Ranibizumab PDT with verteporfin	No	**Further evidence required** Scientific evidence is insufficient to assess the cost effectiveness of ranibizumab in wet AMD. Monthly tx with ranibizumab improves vision to a substantially higher degree than PDT in follow-up ≤2 y
PBAC,[40] Australia, 2007	PBAC	Ranibizumab PDT with verteporfin PL	No	**Ranibizumab recommended for restricted use** Ranibizumab recommended for tx of subfoveal CNV due to wet AMD as diagnosed by fluorescein angiography. Initial tx to be prescribed by an ophthalmologist pending specific authority approval
Augustovski et al.,[39] Argentina, 2007	Instituto de Efectividad Clínica y Sanitaria	Ranibizumab Pegaptanib Laser photocoagulation PDT with verteporfin	No	**Ranibizumab recommended** Ranibizumab and pegaptanib are effective for the tx of all wet forms of AMD, and can be considered as first line. Ranibizumab is superior to pegaptanib as it not only delays or decreases vision loss, but also causes a great number of pts to have a significant vision improvement; use of these agents should be limited to subfoveal or juxtafoveal lesions, where laser photocoagulation is not applicable; there is not adequate evidence on the usefulness of bevacizumab
SMC,[41] Scotland, 2007	SMC	Ranibizumab PDT with verteporfin	No	**Ranibizumab recommended** Ranibizumab is recommended for the tx of wet AMD. It should be stopped if visual acuity falls persistently below 6/60 during tx
SMC,[65] Scotland, 2006	SMC	Pegaptanib PDT with verteporfin	No	**Pegaptanib recommended for restricted pt subset** Pegaptanib is recommended for the tx of wet AMD in pts with visual acuity between 6/12 and 6/60 (inclusive) and should be stopped if visual acuity falls below 6/60 during tx or where severe visual loss is experienced
PBAC,[66] Australia, 2005	PBAC	PDT with verteporfin PL	No	**PDT with verteporfin recommended for restricted pt subset** PDT is recommended for subfoveal CNV secondary to wet AMD where the CNV comprises predominantly (≥50%) classic lesions as defined by fluorescein angiography

Continued next page

Table V. Contd

Reference, country, y	HTA body	Treatments evaluated	Original health economic analysis?	Recommendation
AETMIS,[13] Canada (QC), 2004	AETMIS	PDT with verteporfin No tx	Yes	**PDT with verteporfin recommended for restricted pt subset** PDT is recommended as effective in slowing the progression of subfoveal wet AMD with predominantly classic CNV or pure occult CNV. The estimated budget impact for a Québec cohort is acceptable if the improvement in QOL is taken into account
Meads et al.,[18] UK, 2003	National Institute for Health and Clinical Excellence	PDT with verteporfin PL	Yes	**PDT with verteporfin recommended for restricted pt subset** PDT is recommended for the tx of wet AMD with a confirmed diagnosis of classic with no occult subfoveal CNV and best-corrected visual acuity 6/60 or better; PDT is not recommended for the tx of pts with predominantly classic subfoveal CNV associated with wet AMD
Oliva,[67] Spain (Catalunya), 2006	Catalan Agency for Health Technology Assessment and Research	PDT with verteporfin	No	**PDT with verteporfin permitted for restricted pt subset** PDT is recommended for predominantly classic subfoveal CNV and occult CNV with no classic component caused by AMD and when the neovascular process is active. Precise and careful pt selection is recommended prior to the tx and when the neovascular process is active. HR-QOL impact remains to be determined
SBU,[64] Sweden, 2001	SBU	PDT with verteporfin	No	**Further evidence required** There is no evidence concerning pt benefits in the long term or the cost effectiveness of tx. It is important that pts in Sweden are monitored in a uniform way that allows assessment of the ongoing tx results
MSAC,[35] Australia, 2001	MSAC	PDT with verteporfin PL	Yes	**PDT with verteporfin recommended for restricted pt subset** PDT is recommended only for pts with predominantly classic (>50% classic) subfoveal CNV secondary to wet AMD
ANAES,[68] France, 2001	ANAES	PDT with verteporfin Laser photocoagulation Transpupillary thermotherapy Surgical tx External radiotherapy	No	**Laser photocoagulation recommended** For the exudative forms of AMD, the tx of choice for perifoveal lesions is laser photocoagulation; for subfoveal lesions, the only applicable form of tx is PDT when visual acuity is 2/10 or better
Meads and Moore[69] UK, 2003	West Midlands Health Technology Assessment Collaboration	PDT with verteporfin PL	Yes	**PDT with verteporfin not recommended** PDT with verteporfin was not cost effective for tx of wet AMD; incremental cost per QALY gained was estimated at £120 095 (estimate range £164 579–79 247) when taking the cost of blindness into account

AETMIS = Agence D'évaluation Des Technologies Et Des Modes D'intervention En Santé; **ANAES** = National Agency For Accreditation And Evaluation In Health; **CDR** = Common Drug Review; **CNV** = choroidal neovascularizton; **HR-QOL** = health-related QOL; **MSAC** = Medical Services Advisory Committee; **PBAC** = Pharmaceutical Benefits Advisory Committee; **PDT** = photodynamic therapy; **PL** = placebo; **pt** = patient(s); **QOL** = quality of life; **SBU** = Swedish Council on Technology Assessment in Health Care; **SMC** = Scottish Medicines Consortium; **WTP** = willingness to pay.

pegaptanib was evaluated separately by the Scottish Medicines Consortium, but was recommended for use only in a restricted patient subset (defined by baseline visual acuity).[65] Eight older HTAs conducted before the availability of ranibizumab and pegaptanib were identified for PDT with verteporfin; of these, five (from Australia, Canada, Spain and the UK) recommended PDT only in a restricted patient subset (predominantly classic CNV, based on the available clinical evidence),[13,18,35,66,67] and the remaining three (from France, Sweden and the UK) concluded either that PDT was not cost effective compared with other options or that further cost-effectiveness evidence was required.[64,68,69]

7. Discussion

In the Western world, AMD is the leading cause of severe central vision loss to the point of legal blindness or worse in people aged ≥50 years.[70,71] Wet AMD thus has a major impact on patient QOL and imposes a significant burden on healthcare systems.[72] We conducted a systematic review of studies evaluating the cost effectiveness of treatments for wet AMD in the published literature and in HTA reviews, which identified a broad range of analyses of the most commonly used therapies for wet AMD (ranibizumab, pegaptanib, bevacizumab and PDT with verteporfin), along with a smaller number of analyses of other treatments, such as laser photocoagulation and antioxidant vitamins. Although there was considerable variation in the methodology for cost-effectiveness modelling across studies, ranibizumab was consistently shown to be a cost-effective therapy for wet AMD. This finding was supported by the conclusions of independently conducted HTA reviews; of seven identified HTA appraisals that included ranibizumab, six (including HTA bodies in the UK, Canada and Australia) recommended that ranibizumab was cost effective for the treatment of wet AMD.[2,25,28,39-41]

The majority of published cost-utility analyses compared ranibizumab, pegaptanib or PDT with verteporfin with no treatment, usual care or best supportive care. For ranibizumab, four of the five studies identified (including HTA appraisals from the UK and Canada and cost-utility studies from the US and Germany) showed ranibizumab to be cost effective depending on time horizon; the cost-utility studies showed ICERs below commonly accepted thresholds (e.g. £30 000 or $US50 000 per QALY gained);[2,24,27,37] a fifth study in the US showed that ranibizumab was dominant over usual care when caregiver costs were taken into account, but not cost effective when caregiver costs were excluded.[26] Of five pegaptanib studies, one UK analysis found pegaptanib to be clearly cost effective versus best supportive care over a 10-year time horizon;[23] the other four studies (including a UK HTA) showed that the cost effectiveness of pegaptanib varied considerably depending on the stage of disease and time horizon.[2,11,21,22] Nine studies provided cost-utility analyses of PDT with verteporfin compared with no treatment, usual care or best supportive care, reflecting that this is an older treatment option for wet AMD. Over time horizons of ≥5 years, PDT was shown to be cost effective depending on model perspective in five studies (two in the US, two in the UK and one in Canada);[11,13-15,20] two studies (one in Canada, one in Australia)[17,19] showed that PDT was of borderline cost effectiveness in patients with good baseline visual acuity but not cost effective in patients with greater impairment at baseline; by contrast, two other studies (a UK HTA analysis and a study in Switzerland) showed that PDT was not cost effective.[16,18]

Few published studies have compared active treatments, but the results of six such studies that were identified clearly suggested ranibizumab to be a cost-effective current option for the treatment of wet AMD. Thus, HTA appraisals from the UK and Canada, and a cost-utility study in Spain suggested that ranibizumab was cost effective relative to pegaptanib or PDT with verteporfin.[2,28,30,31] The Canadian HTA assessment and a separate cost-utility study both suggested that pegaptanib was cost effective relative to PDT with verteporfin.[21,28] A US study by Fletcher et al.,[29] comparing the cost effectiveness of all three treatments with best supportive care, showed a lower ICER for ranibizumab relative to the other treatments, with PDT having a lower ICER

than pegaptanib. However, because of the 2-year time horizon used, all treatments were associated with ICERs of >$US500 000 per QALY gained, well in excess of accepted thresholds for cost effectiveness. This study illustrated clearly the importance of time horizon as a key determinant of cost effectiveness, as would be expected given that most wet AMD treatment costs are incurred in the initial treatment period, whereas benefits such as avoiding blindness are gained over a considerably longer timeframe. Across the studies included in this analysis, a time horizon of ≥5 years was generally necessary to demonstrate cost effectiveness at standard WTP thresholds of clinically more efficacious, but more expensive, newer treatments compared with less efficacious, older options.

In addition to cost-utility analyses, most studies included one or more of a variety of additional cost-effectiveness outcomes. The most common outcome was cost per vision-year saved, although others (such as cost per Snellen line-year of life-expectancy and cost per case of blindness prevented) were also evaluated. The absolute costs of such outcomes are difficult to interpret, and the variation in methodology, perspective and time horizon between studies makes cross-study comparisons perilous. Nevertheless, the general trend was for ranibizumab to be more cost effective than other treatment options. For example, in the analysis conducted by Smiddy,[32] the calculated cost per Snellen line-year gained compared with no treatment over a lifetime in predominantly or minimally classic CNV was lowest for ranibizumab under the PrONTO regimen with 1 year of treatment ($US344); this was lower than the corresponding average values observed for PDT with verteporfin ($US448) or pegaptanib ($US1248).

It is important to note that the PIER regimen, where ranibizumab is administered less frequently than with the MARINA and ANCHOR regimens, was consistently shown to have a lower cost per QALY gained than the monthly dosing regimens of MARINA and ANCHOR. However, mean visual acuity of patients treated using the PIER regimen is not improved from baseline after 12 months of treatment, whereas mean visual acuity is increased using the MARINA or ANCHOR regimens.[8,9,42] Finding a dosing regimen that maintains the high level of efficacy seen in the MARINA and ANCHOR studies while minimizing costs would benefit both patients and healthcare providers. The PrONTO study, which used an Optical Coherence Tomography-guided variable-dosing regimen, resulted in visual acuity outcomes similar to the MARINA and ANCHOR studies, with fewer intravitreal injections over a 2-year period.[43] Further investigations will be required to determine whether this is a cost-effective option.

Almost all of the studies identified in our review utilized a second-eye treatment model for assessing the cost effectiveness or cost utility of the treatments under investigation. A second-eye model is simpler, as it assumes that the first eye has already lost vision, hence visual acuity benefits are accrued immediately after treatment. By contrast, a first-eye model presumes that a patient does not accrue treatment benefit until the second eye is affected (at which point vision is deteriorating, and treatment in the first eye becomes critically important to the patient). A second-eye model will therefore predict greater value from treatment than a first-eye model, as demonstrated by the lower ICERs in studies that compared both models.[24] On the other hand, a first-eye model contains more complexity and uncertainty because it must incorporate modelling of progression from unilateral to bilateral disease. Most clinical studies in wet AMD have evaluated a mixture of first- and second-eye cases, reflective of clinical practice; the MICMAC observational study conducted in France, Germany and Italy showed that the use of laser photocoagulation and PDT was similar in first- and second-eye cases.[73]

The growing off-label use of bevacizumab has complicated the management of wet AMD. Intravitreal administration of bevacizumab for wet AMD remains controversial given the absence of high-quality, RCT evidence for the comparative efficacy and long-term safety of this agent relative to established treatments for wet AMD, such as ranibizumab. In addition, bevacizumab cost data are complicated by external and unregulated pricing factors, such as those related to compounding

pharmacies. As would be expected given the lack of robust clinical and economic data for bevacizumab in this indication, our review identified no studies that have properly evaluated the cost effectiveness of bevacizumab in wet AMD. The available published analyses were based only on the lower cost of bevacizumab and assumed equivalent efficacy to ranibizumab. Until rigorous clinical evidence is provided, demonstrating the comparative efficacy and safety of intravitreal bevacizumab relative to approved treatments for wet AMD, it is not appropriate to assume that bevacizumab would be cost effective compared with ranibizumab based on the lower acquisition cost alone. Moreover, while it is hoped that ongoing trials such as CATT[50] and IVAN[74] will be sufficient to establish the efficacy (and in the case of IVAN, the safety profile) of bevacizumab compared with ranibizumab, it is uncertain whether these outcomes will be adequately shown.

8. Conclusions

Our systematic review finds that ranibizumab has consistently been shown to be cost effective for wet AMD in comparison with other currently approved wet AMD therapies (usual care including PDT with verteporfin or pegaptanib), as judged by the bulk of cost-effectiveness data from the published scientific literature and supported by the independent economic assessments of healthcare providers worldwide. Pegaptanib has been shown to be of borderline cost effectiveness, depending on the stage of disease and time horizon. Prior to the launch of VEGF inhibitors, PDT with verteporfin was recommended as being a cost-effective option for the treatment of wet AMD compared with usual/best supportive care at that time.

Acknowledgements

All authors participated in the development and writing of the manuscript, and approved the final article for publication. The authors take full responsibility for the content of the article and would like to thank Dr Annette Keith (Oxford PharmaGenesis™ Ltd) for carrying out the initial literature searches, providing the authors with an overview of the search findings, and collating and incorporating comments from all authors. This editorial assistance was funded by Novartis Pharma AG, Basel, Switzerland. This analysis was supported by Novartis Pharma AG, Basel, Switzerland.

PM has received consultancy fees from Novartis Pharma AG, Pfizer, Allergan and Solvay and has also been paid lecture fees/honoraria by these companies. LA has received an unrestricted grant from Novartis. RW is an employee of Oxford PharmaGenesis™ Ltd, which has received project funding from Novartis Pharma AG. MG and ST are employees of Novartis Pharma AG.

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